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US ARMY MEDICAL RESEARCH LABORATORY

FORT KNOX, KENTUCKY

REPORT NO. 577

ELEVATION OF THE THERMAL THRESHOLD BY EXPERIMENTALLY INDUCED LOCAL VASOCONSTRICTION

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UNITED STATES ARMY
MEDICAL RESEARCH AND DEVELOPMENT COMMAND

10 June 1963

Report Submitted 27 March 1963

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Basic Research in Psychological and Social Sciences
DA Project No. 3A012001B801

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ABSTRACT

ELEVATION OF THE THERMAL THRESHOLD BY EXPERIMENTALLY INDUCED LOCAL VASOCONSTRICTION

OBJECT

To ascertain whether a relationship exists between the condition of the superficial capillary networks and the cutaneous sensory systems and to determine what control problems might be expected in future experimentations in this area.

RESULTS AND CONCLUSIONS

The transport of epinephrine chloride into the human skin by electrical means (iontophoresis) was demonstrated to produce local changes of surface temperature which was related by the theoretically derived curves of Hertzman to a reduction in cutaneous circulation and thus to a reduction in vasomobility. A positive correlation was demonstrated between the calculated decrement in circulation and thermal threshold. These thresholds were statistically higher than those of a normal control area. Non-significant thermal threshold differences in control and experimental areas of the forehead were related to the inexperience of the psychophysical subject at this time in the experiment and to a reported lack of vasomotor innervation of this area. Vibratory thresholds were unaltered by the iontophoresis and supposed reduction in vasomotility.

The results support an independent transducer mechanism for the thermal and tactile sense and emphasize the role of the cutaneous capillary system in the temperature detection process. These data and conclusions may be considered as a tentative test of Nafe's vascular theory of thermal reception.

RECOMMENDATIONS

Further examination of the temperature transducer might best include:

(1) Examine $\Delta I/I$ functions for vasoconstricted and for vasodilated areas.

(2) Electrophysiological examination of smooth muscle thermal responsiveness in a simple system like that of Ascaris lumbricus.

(3) Attempt to directly quantify the capillary circulation by radiotracer or other methods during variations in surface temperature.

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ELEVATION OF THE THERMAL THRESHOLD BY EXPERIMENTALLY INDUCED LOCAL VASOCONSTRICTION

I. INTRODUCTION

In life the subjective experiences, "warm" and "cool," may be produced by local exchanges of energy between the organism and the environment. These exchanges across the organism-environment interface are physically registered as gains or losses in the thermal activity, or "temperature," around a relatively stable thermal ground state called physiological zero. Subjectively, this zero points sets the reference level from which the judgment of warm or cool is made. Compared to the other human sensory systems the "floating" reference level for the thermal sense is unique. Many other senses including vision (1), audition (2), and olfaction (3), have been demonstrated to possess thresholds which approach the zero input energy level.

Under equilibrium conditions, where there is no gradient across the interface, the instantaneous thermal reference is determined primarily by the condition of the cutaneous vasculature. The role of cutaneous circulation in temperature regulation and the modification of local thermal reception has been described as a complex, if passive one, by Bazett (4), Hensel (5), and Lele et al (6). Nafe (7) and Kenshalo and Nafe (8), have proposed a more active relationship between vascular and thermal sensory events. The established thermal lability of smooth muscle was theorized as a mechanical transducer which activates attached afferent endings (9). These researchers placed the burden of quality discrimination in the central projection areas where interpretation of patterns of afferent inflow occur.

Such a system requires mechanically responsive smooth muscles in the superficial vascular structures, and makes the implicit assumption that inhibition of vascular motility results in a loss of thermal sensitivity. This research attempted to test this assumption by reducing the ability of the cutaneous vessels to respond to thermal influences.

II. METHOD

Research into cutaneous circulation by Cooper, Edholm, et al (10, 11) and Edholm, Fox, et al (12) has yielded a method for reducing superficial circulation through the action of epinephrine (adrenalin chloride) electrically infused into smooth muscle. The reported effectiveness of iontophoretically induced vascular "clamp" ranges from 60 to 80%. The electrical infusion technique as modified for local vasoconstriction in the present experiment is as follows.

The subject, a Caucasian male 28 years of age with no previous history of vascular disease, was introduced into a constant temperature chamber not less than 30 minutes prior to the beginning of experimentation. During the eight experimental periods the temperature of the chamber ranged randomly from 21.0°C (Celsius) to 22.8°C. While the subject was habituating to his environment, the experimenter prepared a fresh solution of adrenalin chloride, which was adjusted to pH 4.5 by the addition of phosphate buffer. The solution was brought to 32°C and stored in a vacuum bottle. The subject was then fitted with two wick type electrodes. The ground electrode consisted of a 4 X 6 in. cellulose sponge which had been split in half. The left arm was sandwiched at the wrist within the sponge which was saturated with normal saline. Copper conductors were wrapped around the exterior of the sponge and connected to the negative of the EMF source, a 45 volt battery. The positive pole of the battery was connected through a voltage divider and milliammeter to the positive electrode sandwich. The elements of this electrode were composed of a 2.5 cm^2 stainless steel plate which rested upon a 0.25 in. thickness sponge reservoir of equal dimensions and finally upon a 2.5 cm^2 section of blotter paper. The blotter paper element rested upon the experimental skin area. It was possible to saturate the reservoir with buffered adrenalin chloride and drive the chemical electrically into the skin by passing current through the system. Two concentrations of adrenalin were used during the experiment. The first four sessions on the forehead utilized a 1 in 2000 solution and the second four sessions on the forearm, a 1 in 1000 solution. The rate of diffusion was controlled by the subject through the voltage divider. He was instructed to increase the current gradually during the first five minutes to reach a maximum tolerable level. This level, usually less than 5 ma, was maintained for 15 minutes and the current was then gradually reduced to zero. The entire infusion required a 25 minute period. Two criteria were used as indices of satisfactory infusion. Immediately under the active electrode and upon its removal, a marked leukomia of the tissue was observed. If this was coupled with a temperature drop localized to the infused area of at least 0.5°, it was assumed that a moderately successful vascular clamp had been achieved. Hertzman (13) has reported that a 1° change in surface temperature, when ambient temperature equals 24°C, may signify a reduction in cutaneous blood flow of 25 to 40% of the normal value.

Prior to infusion the vibratory threshold was compared between the experimental area and randomly selected, adjacent control areas. A second series of vibratory thresholds were made following the infusion. The parameters of the vibratory stimulus are diameter, 0.75 cm; frequency, 50 c.p.s.; and pressure, 80 gm. The intensity of

vibration is reported in decibels referenced to an input of 1 milliwatt into a 600 ohm impedance. Similar checks on vibratory sensitivity were made on both the forearm and the forehead, each experimental series.

Immediately following the vibratory check, the area under study was irradiated by near infrared. The subject initiated the exposure by depressing a signal key. Release of the key, which also controlled a time clock, indicated the first warm experience. Measures of infrared threshold were taken in both the experimentally infused area and the adjacent normal control area. The irradiated skin segment had been covered with a thin coat of India ink following the technique previously described by Hardy. Stimuli were produced by a 150 watt Sylvania type DFA projector lamp. Operated at a regulated 150 watts, maximum input, the emission curve of this lamp approximates a Gaussian function which peaks at 1.2μ. For forehead stimulation the lamp was used at three intensities with the focal diameter of 1 cm. For forearm stimulation, three other energies were used at a focal diameter of 0.7 cm. Calibration of the stimulator was by means of a vacuum Leslie cube like that previously described by Dawson (14) and by Hardy (15). Those powers produced for stimulation of the forehead were 26.7, 43.7, and 112.0 mcal/sec/cm^2. Less intense stimulation was applied to the forearm. These were measured as 7.7, 12.0, and 32.7 mcal/sec/cm^2. Threshold were recorded in terms of time from onset of stimulation to report of threshold by the subject to the closest one hundredth second. It was then possible to calculate total energy which had been delivered to produce threshold in mcal/cm^2. The forehead and forearm experiments were done consecutively. Twenty-eight experimental measures were taken for the forehead with 22 control measures. The forearm measures included 47 experimental and 48 control thresholds. Each daily session contained the three energy levels for that site, presented randomly. Experimental and control trials occurred in blocks of three or four alternately.

The same routine was followed each day. First, the subject was allowed to adjust to the room temperature for one-half hour. During this time the experimenter compounded a fresh solution of adrenalin solution. The diffusion then followed taking approximately 25 minutes. Vibratory threshold measures were made just prior to and just preceding the infusion in both the control and experimental areas. After the second vibratory threshold series, infrared stimulation was begun. Measurements of the temperature at the stimulus site were made by micro thermistor monitors which were imbedded just beneath the surface of the cutis and anchored by flexible collodion. Following

stimulation these enabled the experimenter to determine when the temperature of the exposed area had returned to the normal level. Frequently this was a rather slow procedure. Therefore, the daily experimentation was limited to a 3 hour session which included both the preparatory procedures and the threshold measures themselves.

III. RESULTS

Vibratory threshold measures were taken at six randomly selected points in the control and experimental areas of the forehead and forearm prior to and immediately following the adrenalin infusion. The results lend themselves to statistical analysis by means of the Kruskal-Wallis analysis of variance (16). The data for each site were cast into four columns, the values of H were computed and corrected for ties. For large samples the values of H are distributed approximately as Chi^2 with the number of degrees of freedom equal to one minus the number of groups. For three degrees of freedom, a value of H equal to or greater than 5.99 must be achieved for significance at the 5% level. The largest value of H calculated between these groups was 1.40.

Beuttner (17) has mathematically treated the problem of a changing skin temperature following exposure to intense thermal irradiation. A modification of his equation has been published by Hendler et al (18), who attempt to describe the changes of skin temperature produced by moderate infrared input at a heavily absorbing surface. This equation may be seen as equation one. T_s is the skin temperature at any time

$$T_s = T_{so} \frac{2 \alpha Q \sqrt{t}}{\sqrt{\pi}\ kpc} \quad (1)$$

after the start of irradiation, T_{so} is the initial temperature of the tissue prior to irradiation. The value α is the net radiation absorbance of the skin surface for the particular emission spectrum of the source of radiation. Q is the radiation flux in $mcal/cm^2/sec$ and t is the time of exposure. The value for kpc may be considered the coefficient of thermal inertia for surface heating. It is developed from k, the specific thermal conductivity of the tissue, c, its specific heat, and p, its density. Empirically derived values for kpc in $mcal/cm^4/sec^2$ have been reported by Hardy, Goodell and Wolff (19), Oppel and Hardy (20), Beuttner (21), and Lipkin and Hardy (22). Average values found ranged from 100 to 120×10^{-5}. The mean value of kpc most recently reported by Hardy, 108×10^{-5}, was assumed the correct one for purposes of this research.

For thermal threshold studies the variable of primary interest is the temperature increment associated with the first experience of warm. Then, T_{so} may be removed from the equation and Δ T be set equal to the second term of equation two. Hendler (18) has reported that the net

$$\Delta T = \frac{2 \alpha Q \sqrt{t}}{\sqrt{\pi \, kpc}} \tag{2}$$

absorbance of normal human skin in the near infrared is approximately 0.98. For blackened skin, as in the present research, it was assumed that the net absorbance would approach unity. Thus, the term $\underline{\alpha}$ may be removed from equation two. Also, since only one tissue was under consideration, the value of kpc reported by Hardy was assumed to be a constant. The simplified thermal increment equation three was used to calculate temperature changes associated with threshold for the present study. The only information required for calculation of Δ T is the input flux intensity for which the stimulator had been previously calibrated and the time required for the report of threshold.

$$\Delta T = \frac{2 Q \sqrt{t}}{\sqrt{k}} \tag{3}$$

The threshold temperature Δ T calculated from equation three may be seen for each of the three stimulus intensities and for each of the two stimulation sites in Figure 1. The limit marks at the data points indicate the standard error of the mean in degrees. Table 1 is the results of an analysis of variance between the thresholds in mcal/cm^2 for each experimental site. The stimulus area or the forearm was 0.385 cm^2 and for the forehead, 0.785 cm^2. It may be observed that significant F values were obtained for the forearm experiment where the larger number of threshold measures were taken. The interaction term is insignificant. All the results for the forehead experimentation yield insignificant F values. The data upon which the analyses were performed were calculated in terms of total mcal/cm^2 doses delivered to the test area between the onset of stimulation and the signaling of threshold by the subject.

For this experiment it was particularly desirable to attempt to relate the change of experimental threshold following vascular immobilization to the degree of vascular immobilization. Hertzman (13) has developed a theoretical curve which relates surface temperature to

the cutaneous blood flow in $L/M^2/Hr$. This particular curve, which is a member of a family of three presented in Hertzman's Figure 1, assumes that the relationship between surface temperature and blood flow is complicated by the fact that heat losses from the surface of the body tend to remain constant over a considerable range of environmental conditions.

The reductions in cutaneous blood flow in $L/M^2/Hr$ were estimated from Hertzman's relation by the association of flow rate with the change in surface temperature produced by the iontophoresis technique. In Figure 2 these are presented as the abscissa plotted against the ratio of experimental warm threshold minus the mean control warm threshold to the control warm threshold. An ordinate value of zero then would indicate that the experimental mean and control mean were the same. Positive ordinate values indicate an increase in experimental mean threshold and negative values indicate a decrease in mean experimental threshold related to the control threshold. Many arguments may bear against measurement of surface temperature with thermocouples, thermistors, and other single point measuring devices. Obviously with such instruments, bias may be injected by the proximity of the surface blood vessels where readings indicating an integrated temperature over a large area are the desired measure. The data are presented in the forms of histograms lumped for large portions of the abscissa variable because of losses in precision due, probably, to punctuate measures of surface temperature.

IV. DISCUSSION

Iontophoretic epinephrine infusion of local skin areas, rather than the whole arm or whole leg, was carried out in this experiment for several reasons. Difficulty was anticipated in the quantification of the degree of vascular immobilization. Also, the vast area presented by a whole extremity might lead to a confusion on the selection of the point for thermal stimulation. Increases in systemic adrenalin content were also anticipated to produce difficulties in human psychophysics. Cooper et al (10) indicate considerable precaution against this problem in their study on the cutaneous circulation in whole limbs which had been experimentally vasoconstricted. Since it has been demonstrated (12) that deep circulation is largely constant while only the superficial vessels respond to temperature and adrenalin, it was deemed best to undertake an initial study with local vasoconstricted areas.

The forehead data of Figure 1 show an elevated warm threshold for the vascular clamped experimental area for the higher two stimulus intensities. However, a reversal of effect, which is largely unexplained, may be seen at the lower intensity. In retrospect, it is likely that the forehead and other facial areas are not the most desirable sites for thermal psychophysics. Hertzman (23) has written that there appears to be a lack of vasoconstrictor innervation in the head and neck while the results of Hardy and Oppel (24) suggest that the trigeminally innervated areas are perhaps hypersensitive to thermal stimuli relative to other body areas. These facts may set the forehead apart from representative cutaneous areas. The forearm, which has been used extensively by Kenshalo (25) and Cooper et al (11) in studies of thermal psychophysics and vascular phenomena did not exhibit the low intensity reversal. At this site the analysis of variance was significant for both stimulus intensity levels and treatments.

It is possible to criticize the "vascular immobilization" procedure for psychophysical studies of thermal experience on grounds that reduced blood flow to the cutaneous areas probably results in altered peripheral nerve responsiveness. It was for this reason that the vibratory stimulus series was made. The total lack of significant differences between the experimental and control areas for vibratory threshold would indicate that this is not a valid criticism. It must not be assumed that iontophoresis eliminates surface peripheral blood flow. All previous quantifications of blood flow alterations following adrenalin infusion indicate efficiencies > 50-70% (12). It is of interest in this context, however, that thermal threshold alterations are easily demonstrated with no indication of alteration of vibratory threshold. Such a finding supports the view that the transducer mechanisms are not identical.

The subject in this study was required to report the first "warm" experience as threshold. In difference threshold studies Kenshalo (25) has shown that there is a gradual increase in the threshold for warm at adapting temperatures less than 36°C. Thus, it may be argued that the elevation in threshold seen following iontophoresis is a result not of changes in vascular responsiveness but simply an alteration in the adapting temperature. For the forehead the mean experimental area temperature, which for purposes of discussion may be called adapting temperature, is 31.45°C. The mean control area temperature for the forehead was 32.64°C; a net decrease of 1.22°C. Entering the previously discussed curve of Hertzman's, which relates local surface temperature to cutaneous blood flow rate (13), it may be found that the decrease in flow in this experimental area was 3.5 $L/M^2/Hr$. Kenshalo's research indicates that such a change at adapting

temperature would increase the threshold 0.3°C on the forearm (25). The mean forehead alteration produced by iontophoresis indicates a threshold increase of 0.5°C. For the forearm the average temperature of the experimental areas was 28.57° while the control mean was 29.92°. Unfortunately, Kenshalo's difference threshold curves do not extend to adapting temperatures lower than 30°C. Extrapolation from Kenshalo's 30° adapting level would predict a 0.6° elevation in threshold for the 29.9° adapting temperature. In this case, the threshold elevation in the iontophoretically infused area is less than would have been predicted in terms of changes in adaptation. It must be concluded that there is little agreement between predicted elevations in threshold produced by thermally adaptated local areas and those produced by changes in surface temperature following partial vascular clamp. It should be recalled, however, that Kenshalo's stimulus, was a tactile one and thus produced a conducted thermal stimulus, while that in this report was by radiated infrared. A major difference between the adapting temperature from Kenshalo's research and that produced by iontophoresis is found in the superficial gradients. Induced lowering of adapting temperature by contact stimuli increases the interface-vascular level thermal gradient while iontophoretically reduced adapting temperature reduces the gradient for an equivalent superficial change in temperature.

The comparison between the degree of thermal elevation and threshold in the control area against the degree of circulatory reduction indicates a progressive elevation of threshold in the experimental area with altered blood flow. Only two series of measures were taken in experimental areas where the reduction of blood flow was greater than 4.5 $L/M^2/Hr$. It is interesting that in each of these measures the experimental threshold was equal to or less than the control thresholds. It is not known if these are due to systemic effects where high adrenalin concentrations produced altered nerve excitability or whether there are basic alterations that occur in the capillary walls at high adrenalin concentrations. Further experimentation is presently underway in an attempt to describe the threshold curve with greater reductions in cutaneous flow. Limitations are imposed by the ability of the subject to tolerate greater current densities or higher adrenalin concentrations.

The data which have been presented are considered indicative of a selective effect for the amount of superficial cutaneous circulation between local thermal and vibratory thresholds. Since precise quantification of cutaneous flow and vascular mobility has not been obtained, the modest thermal changes which have been demonstrated consistently

to accompany localized large reductions in circulation may be tentatively assumed to support the original hypothesis of Nafe (7), in which the peripheral vascular structures are suggested as primary in the transduction of cutaneous temperature change into afferent information.

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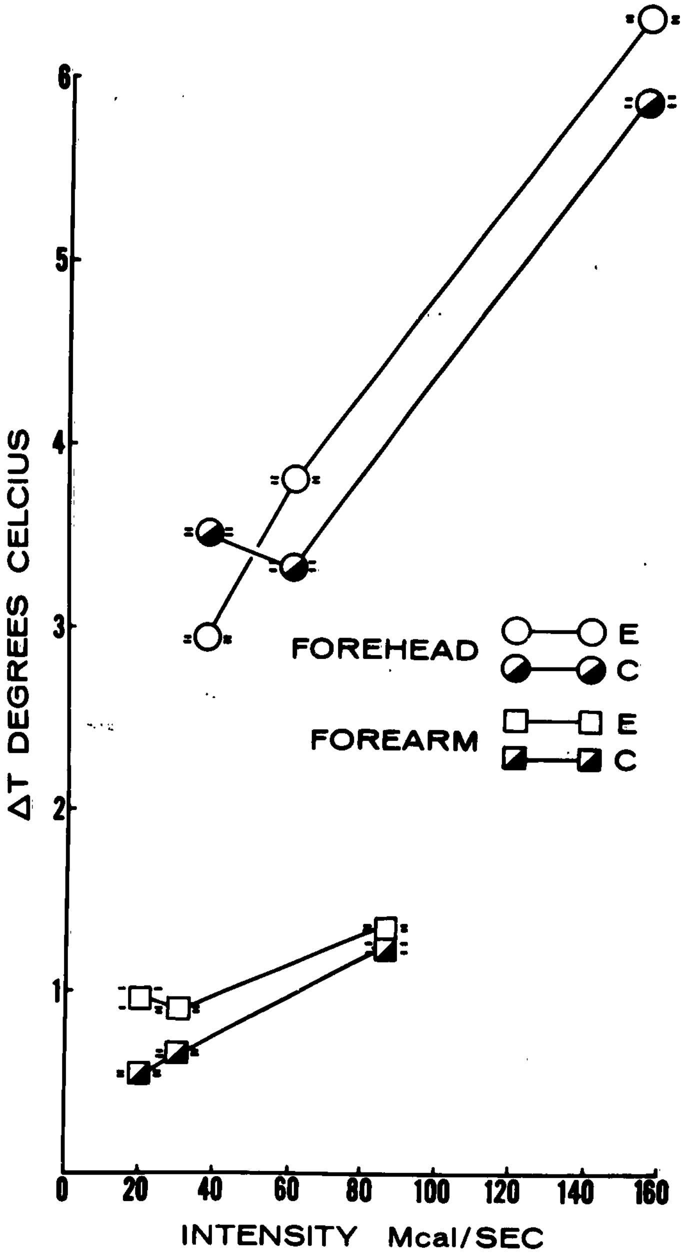

Fig. 1. Mean temperature thresholds calculated from equation three for the two stimulation sites and two conditions. E indicates the experimental or "clamped" site measures and C the normal control. The limit marks define the standard error of the mean values for each point.

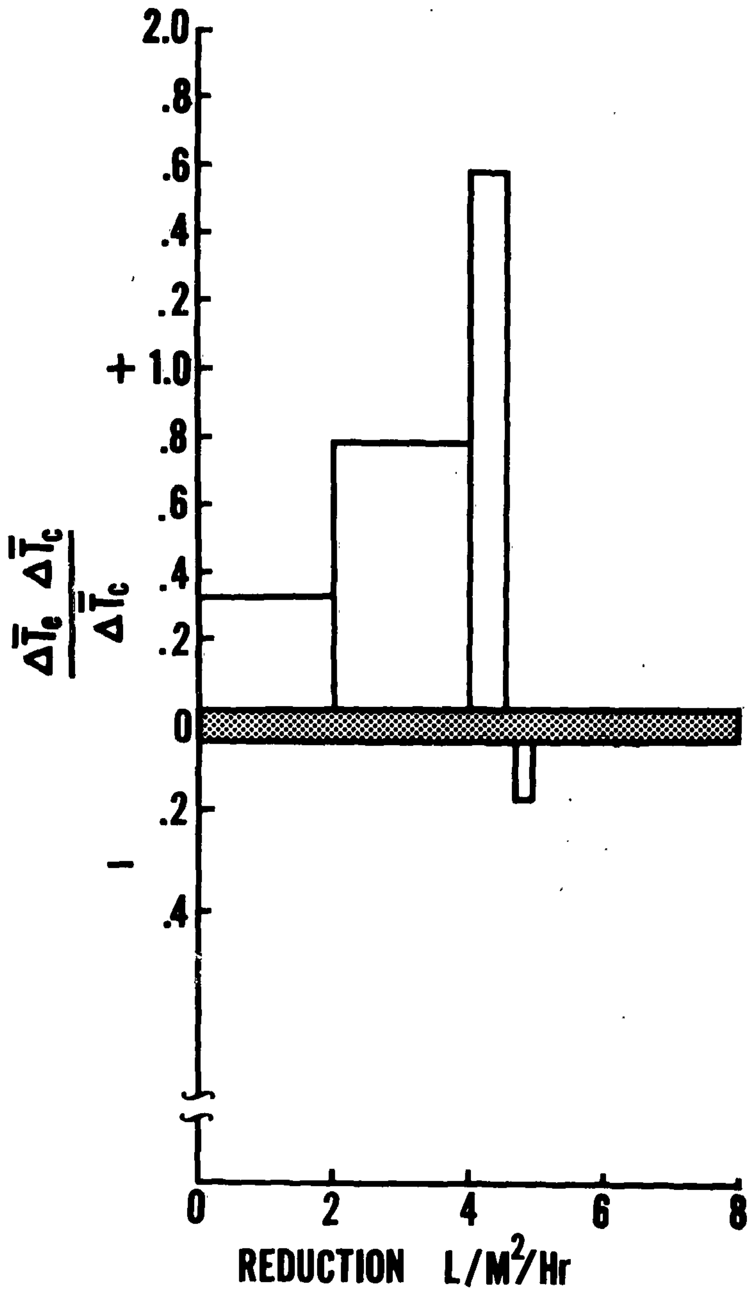

Fig. 2. The relative change of the mean experimental warm threshold with estimated efficiency of vascular clamp measures as the reduction in cutaneous circulation. Lumping of the abscissa variable was necessary due to large variations in threshold with calculated flow rate.

TABLE 1

SUMMARY TABLE FOR ANALYSIS OF VARIANCE

Variance Source	df	Sum of Squares	Mean Square	F	P
		Forearm			
Intensity	2	4502.32	2251.18	4.66	<.05
Treatment	1	8835.57	8835.51	18.29	<.001
(cells)	(5)	(15831.20)			
Interaction	2	2493.24	1246.62	2.58	<.10
Within Cells	89	42994.93	483.08		
Total	94	58826.13			
		Forehead			
Intensity	2	42215.80	21107.9	1.10	>.20
Treatment	1	2225.20	2225.2	1.17	>.20
(cells)	(5)	(122994.20)			
Interaction	2	58553.20	29276.6	1.54	>.20
Within Cells	47	891750.80	18973.4		
Total	52	1014745.00			

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2. Cutaneous sense receptors
3. Superficial circulation

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